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**Title** Treatment of active Crohn's disease with exclusive and partial enteral nutrition: a pilot study in adults.

**Running title.** Enteral nutrition in active adult CD

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**Abstract**

**Background and Aim:** Enteral nutrition is not commonly used for the treatment of adults with active Crohn's disease, despite patient interest in nutrition-based alternatives to

corticosteroids and evidence of efficacy in paediatric Crohn's disease. The aim of this study was to assess the impact of two different enteral nutrition regimens on disease symptoms, nutrition and inflammatory markers in young adults with active Crohn's disease.

**Methods:** A prospective non-randomized pilot study of adults aged 16 – 40 years with active Crohn's disease on endoscopy or imaging was undertaken. Patients were sequentially recruited to use two weeks of exclusive enteral nutrition followed by either six weeks of exclusive enteral nutrition or partial enteral nutrition with usual diet. Assessments of disease symptoms, nutrition and inflammatory markers were undertaken at baseline and throughout the treatment.

**Results:** Thirty-eight patients with active disease were recruited. Thirty-two (84 %) patients completed two weeks of exclusive enteral nutrition and had significant improvements in disease symptoms ($p$=0.003), serum c-reactive protein ($p$=0.005), insulin-like growth factor-1 ($p$=0.006) and faecal calprotectin ($p$ = 0.028). During the following six weeks, 21 patients continued exclusive enteral nutrition (14 (67%) completed treatment) and 11 patients used partial enteral nutrition (9 (82%) completed treatment). Initial improvements in symptoms, c-reactive protein and nutrition markers were sustained over the next six weeks on both treatments. Faecal calprotectin non-significantly increased in 5/9 patients who used partial enteral nutrition and at week eight faecal calprotectin was greater than 500µg/g in 9/14 and 7/9 patients who used exclusive or partial enteral nutrition respectively. There was no significant difference in clinical outcomes between the two groups at week eight.

**Conclusion:** Two weeks of exclusive enteral nutrition significantly improved disease symptoms, nutrition and inflammatory markers. Further treatment with exclusive or partial enteral nutrition maintained initial improvements.

**Keywords:** Crohn's disease, enteral nutrition, faecal calprotectin, IGF-1

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## Introduction

Crohn's disease (CD), an incurable inflammatory bowel disease, can develop at any age.[1] Intestinal inflammation may present clinically as abdominal pain, increased frequency of loose bowel motions, and/or biochemically with elevated serum and fecal inflammatory markers.[2] There are many pharmaceutical and surgical treatments for active CD.[3, 4] Nutrition based treatments, the most common being exclusive enteral nutrition (EEN), is recommended as a first line therapy to treat active paediatric CD.[5] EEN is now commonly used to treat active CD in children and adolescents in New Zealand (NZ),[6] Australia,[7] Asia,[8] Canada,[9] and Europe.[10] Adults with CD are interested in nutrition based alternatives to corticosteroids,[11] and EEN is regularly used in Japan,[12] and increasingly in China,[13] to treat adults with active CD. For adults living in Western countries, EEN is not currently recommended as a first line treatment for active CD.[2, 14]

Previous studies of EEN to induce CD remission in adult patients have provided variable results.[15] One of the reasons cited for the variability in outcomes is the poor palatability of nutrition formulas and poorer adherence to the exclusive regimens.[15] Partial enteral nutrition (PEN) may help alleviate issues with adherence to EEN: this approach has been trailed in children and adolescents, again with variable results.[16-18]

In the paediatric age group, EEN offers patients benefits over and above the induction of disease remission, including high rates of mucosal healing, which are not achieved with corticosteroids.[19] Faecal calprotectin (FC) has been suggested as a biomarker of mucosal healing due to its moderate correlation with endoscopic assessments of mucosal healing.[20, 21] A few paediatric studies have reported changes in FC following EEN treatment[16, 22-24] but no studies in adult cohorts have reported changes in FC consequent to EEN.

This study aimed to investigate the feasibility and effectiveness of EEN and a novel PEN regimen in young adults with active CD on symptoms of active disease and secondly to document the impact of these treatments on nutrition and inflammatory markers including FC.

## Materials and Methods

### Participants

From May 2013 to December 2015 young adults with active CD aged 16 to 40 years old were invited, at the discretion of the consulting gastroenterologist, to choose between nutrition therapy or corticosteroids to treat active disease. Eligible patients had CD involving at least the ileum and were managed by gastroenterologists in Christchurch, NZ. Patients were excluded from the study if they had isolated colonic disease, active psychological illness or had taken corticosteroids in the last fortnight. Concomitant use of other CD medications did not limit eligibility, however use of corticosteroid medications was not permitted and patients on mesalazine, biological or thiopurine medications needed to be on an existing and stable dose and despite medication use still have active CD. Patients could be started on a maintenance of remission dose of thiopurine medication once established and after four weeks of EN treatment. Active disease was defined as active disease visible by endoscopy or radiology or an elevated FC. Eligible patients were referred to one registered dietitian who obtained their informed consent and managed their nutrition therapy treatment. Ethical approval was given by the NZ Northern B Health and Disability Ethics Committee (ethics reference 13/NTB/11) and the pilot clinical trial was registered with Australia New Zealand Clinical Trial Registry (trial number 363665).

**Enteral nutrition treatments**

Patients were sequentially recruited to use two weeks of EEN followed by another six weeks of EEN or PEN. Patients recruited between May 2013 and February 2015 were offered only EEN and patients recruited from March to December 2015 were offered only EEN followed by PEN. Patients' nutrition requirements were calculated using bioimpedance analysis basal metabolic rate multiplied by a physical activity factor.[25] Patients' nutritional requirements were reviewed fortnightly according to weight change and appetite.

EEN treatment required patients to drink multiple cartons (200 mL) of a polymeric 6.32 kJ/ml (1.5 kcal/ml) oral nutritional formula (Ensure Plus™, Abbott Laboratories, The Netherlands) daily. In addition to the prescribed EN, patients were encouraged to drink additional fluids either as water and/or black unsweetened tea, coffee or herbal tea and avoid all other foods and fluids. EEN was initiated by gradually replacing meals and snacks with EN over a period of three days.

PEN treatment comprised of EN plus one small meal per day (lunch or dinner) of solid food. Lunch and dinner were chosen because these meals are more likely to contain larger amounts of protein and vegetable fiber than breakfast and these meals are commonly shared with friends and/or family. The sharing of food with friends and family was an important aspect because, during the EEN intervention of this study, many patients anecdotally reported EEN to be socially isolating. Patients were encouraged to eat a balanced meal similar to their usual eating habits. After both eight week treatments patients reintroduced usual foods and fluids and reduced EN intake over a period of three days.

**Assessments**

Patients were assessed by the dietitian at weeks 0, 2, 4, 6 and 8. At baseline, demographics, family history, disease phenotype and outcome data were collected. Assessments at all five study appointments included a serum inflammatory marker (CRP), serum nutrition markers (insulin-like growth factor-1 (IGF-1) and albumin, anthropometrics (body mass index (BMI)), intestinal inflammation biomarker (FC) and clinical disease activity (Harvey Bradshaw Index (HBI)).

Serum CRP, albumin and IGF-1 were measured by Canterbury Health Laboratories, NZ using immunoturbidimetry, bromocresol purple assay kit (Abbott C series analyser) and the iSYS automated chemiluminescence immunoassay (Immunodiagnostic Systems, United Kingdom) respectively. FC was batch analyzed from stool stored at – 80°C using a commercial enzyme linked immunosorbent assay kit (BÜHLMANN fCAL, EK-CAL2, Switzerland) as per the manufacturer's instructions. The kit test range was 60 -3600 µg/g. An elevated HBI was not an inclusion criteria to receive EN therapy, therefore improvements in symptom/activity scores were calculated rather than rates of disease remission.

Dietary intake of any food or fluids was self-reported fortnightly. Patients using PEN were asked to provide examples of the meals that they had consumed for their one meal per day. Significant and continued deviations from the protocols resulted in withdrawal from the study. During EEN, non-habitual and small amounts of usual foods/fluids was assumed to have a negligible impact on average energy intake. Nutrient and energy intake during PEN was calculated from a three-day food record using a smart phone/tablet app Evernote©. Patients recorded their intake of food and fluids in real time with photographs of the meal and

any leftovers alongside text descriptions. This electronic food diary has been validated against a paper food diary in young children (unpublished data) but not in adult patients. Nutrient analysis of food records was completed using "Kai-culator" dietary assessment software (version 1.15c Department of Human Nutrition, University of Otago, NZ).

**Statistical analysis**

The results are presented as percentage of responses, medians and ranges. Many of the variables were not normally distributed therefore groups were compared using Mann-Whitney U test, Wilcoxon matched-pairs signed rank test, Fisher's exact test, and Chi-squared test. Statistical significance was present with $p < 0.05$. Statistical tests and graphs were prepared in Prism 6 version 6.05 (GraphPad Software Inc.).

## Results

### Baseline characteristics of the treatment groups

Thirty-eight patients were referred for EN therapy. The first 25 patients were offered two weeks of EEN therapy followed by a further six weeks EEN and the following 13 patients were offered two weeks of EEN followed by six weeks of PEN. The two groups were similar at baseline with the exception of serum albumin which was significantly lower in the PEN group (Table 1).

Patients who had a history of weight loss prior to starting EN treatment (n = 19) had a median IGF-1 SDS which was significantly lower (-1.00 SDS compared with 0.10 SDS, $p = 0.01$) than the median score of patients (n = 19) whose weight was stable prior to treatment. There was no difference ($p = 0.588$) in the median BMI, nor serum albumin ($p = 0.239$) of those who had, and had not, experienced recent weight loss.

Concurrent use of medication, except corticosteroids, was permitted. Eight patients were established on stable doses of medications at baseline but still had active disease (Table 1). No patients were started on mesalazine or biological medications during EN treatment.

**Adherence to treatments**

Figure 1 summarises the flow of patients through the study. Thirty-eight patients started EEN but within a few days of starting, two patients elected to use corticosteroids instead of EEN and another four patients did not tolerate the EN formula (increased diarrhoea or nausea) and therefore did not successfully initiate EEN. After the first two weeks of treatment 21 patients continued on EEN treatment. During the following six weeks, seven patients did not complete EEN treatment: one needed surgery for a small bowel perforation, one reintroduced usual diet at week five in response to work stress, one developed nausea, one deviated significantly from the protocol, one did not respond after four weeks, one had persistent diarrhoea which resolved after stopping the formula and one needed nasogastric tube feeding to meet nutritional requirements and when the tube split opted not to have another tube placed. After the initial two weeks of EEN 11 patients moved onto PEN treatment of which two patients did not complete the treatment: one patient, who had a small bowel perforation and was waiting for surgery, flared after introducing usual food and returned to EEN until the surgery could be performed, and one patient had not responded by week four and was changed to corticosteroid treatment.

There was no significant difference in the proportion of patients who did not complete EEN compared with PEN treatment ($p = 0.502$). However, more adolescent patients (< 18 years

old) did not complete either EEN or PEN treatment than those aged over 18 years (8/15 compared with 3/23, $p = 0.012$).

**Dietary intake**

All patients, except one, reported 100 % compliance with the EEN protocol during the first fortnight of treatment. Thereafter, self-reported intake of usual foods and fluids in the EEN group was minimal, as was intake of foods and fluids apart from the one small meal during PEN treatment. Individuals' total energy intake 6 276 – 13 807 kJ/day (1 500 – 3 300 kcal/day), percentage of estimated energy requirements (% EER) and energy intake per weight varied widely (Table 2) as did the amount of physical activity. The one meal per day during PEN typically consisted of a protein food (red meat, chicken, eggs or fish) with a carbohydrate food (bread, rice, potato, sweet potato or pasta) and cooked or raw vegetables.

**Clinical outcomes**

During the first two weeks of EEN (n =32) median HBI fell from five to three points ($p = 0.003$), median serum CRP fell from 10 mg/L to 5 mg/L ($p = 0.005$), median FC fell from 927 µg/g to 674 µg/g ($p = 0.028$), median IGF-1 standard deviation score improved from 0.0 to 0.05 ($p = 0.006$) and median serum albumin was unchanged at 39.5 g/L (Figure 2).

Fourteen patients used EEN for another six weeks after the initial two weeks of EEN. The improvements in inflammatory markers observed during the first two weeks were sustained to week 8 and there was further improvement in the median HBI ($p = 0.031$). At week 8, 5/14 (36 %) patients had a FC < 500 µg/g compared with 4/14 (29 %) at baseline. Patients using EEN lost weight during treatment, the median BMI fell from 23.7 to 23.3 kg/m$^2$ (W = -79, *p*

= 0.01) although the minimum BMI increased from 18.5 kg/m$^2$ to 19.8 kg/m$^2$ and nutrition markers serum IGF-1 and albumin improved during EEN treatment (Figure 3).

Nine patients used PEN after an initial two weeks of EEN. The median HBI, CRP and FC remained stable after PEN treatment although FC increased in 5/9 patients during PEN treatment (Figure 2) and 2/9 (22 %) had a FC less than 500 µg/g compared with 3/9 (33 %) of patients at baseline. Clinical outcomes in the nine PEN patients were not correlated with volume of EN consumed nor the percentage of total energy from solid food. Patients using PEN had a minimal change in median BMI from 25.2 to 24.7 kg/m$^2$ ($p > 0.05$) and the minimum BMI increased from 16.5 kg/m$^2$ to 18.5 kg/m$^2$.

There were no significant differences in disease activity nor nutrition or inflammatory markers at week eight between patients who used EEN for eight weeks compared with patients who used two weeks of EEN followed by six weeks of PEN.

**Discussion**

This prospective non-randomized pilot clinical trial of EEN and PEN is one of the first PEN studies to include only adults with active CD. This study used a novel PEN regimen which included two weeks of EEN followed by six weeks of PEN with one small meal of usual food. Three studies have been published which used PEN to treat active CD. One of these studies of PEN, which did not include an EEN control group, found that PEN with a specific food exclusion diet effectively induced disease remission in 70 % of children and adults.[18] Whereas, two of the studies found that EEN was superior to PEN with a free diet.[16, 17] In contrast, this study found that PEN with usual food resulted in similar outcomes to EEN at week eight. The lack of difference between the PEN and EEN treatments may be due to the

use of two weeks of EEN prior to the reintroduction of usual food. During the first two weeks of EEN patients had significant improvements in disease activity and inflammatory markers, such early improvements have been observed previously in the adult EEN literature.[13, 26, 27] Further, there is some evidence that patients with newly diagnosed disease respond better to nutrition therapy than patients with long standing intestinal inflammation.[28] The inclusion of mostly newly diagnosed patients and those with mild disease symptoms may have contributed to the comparable outcomes between the two treatments.

Serum IGF-1 is a marker of nutrition status and has been suggested as a marker of disease activity[29, 30] due to its reduced expression in the presence of pro-inflammatory cytokines.[31] An early rise in IGF-1 subsequent to EEN treatment has previously been documented in paediatric IBD studies[30, 32] but has not been reported in adults with CD. Both paediatric studies concluded that early improvements in IGF-1 concentration were due to reduced inflammation rather than purely an improvement in nutrition intake. In this study median serum IGF-1 concentrations increased significantly after two weeks of treatment despite suboptimal caloric intake and reductions in BMI, and corresponded with a reduction in serum CRP and FC. These results support the paediatric IBD observations that IGF-1 is more than just a marker of nutrition status and that improvements in serum IGF-1 concentration may also reflect reduced inflammation.

FC has been suggested as a reliable non-invasive measure of endoscopic disease activity[20, 21, 33, 34] but cut-off concentrations to distinguish active from inactive inflammation remain controversial.[20] Some paediatric studies have reported improvements in FC following EEN[22-24] but to date there are no reports of FC changes consequent to EEN or PEN in

adult cohorts. The current study found a non-significant trend towards improved FC after two weeks of EEN but further treatment with EEN did not result in further improvement in FC concentration. Paediatric EEN studies have also observed that FC often remains elevated post EEN treatment.[22, 24, 35] One PEN study has reported FC, they observed that 14 % children treated with PEN had a FC less than 250 µg/g compared with 45 % treated with EEN and 62 % treated with a biologic medication.[16] Their results, along with the those presented here, suggest that the inclusion of usual food with EN may limit gut mucosal healing.

Patient withdrawal from EN treatment is common in many of the published adult studies and was previously associated with poor palatability of the nutrition formula.[15] This study used a more palatable polymeric formula and as a result no patients withdrew from the treatment due to unpalatable formula. However, non-completion of treatment was higher than anticipated. Most (78 %) of the study cohort were female and 30 % were less than 18 years old. It has previously been suggested that female adolescents with IBD find EN therapy more attractive than corticosteroid treatment, due to the potential negative impact of CS treatment on body image.[36] The high proportion of female participants may represent a selection bias because patients were referred to the study at the discretion of the consulting gastroenterologist rather than systematic referral of all patients meeting the study inclusion criteria. The high proportion of female patients and secondary school age patients is likely to have affected treatment completion. Females and older adolescents are more likely to withdraw from treatment due to non-adherence[10] and this trend was observed in the current study whereby 73 % of adolescents did not complete EN treatment compared with only 26 % of young adults aged 18 years and older. EN treatment may be a more acceptable treatment

for patients who have finished secondary education and moved into the workforce or tertiary education.

A limitation of this study may be the lack of a non-EN control group. Previous randomized controlled trials of EEN and corticosteroids in paediatric patients have shown the two treatments have comparable efficacy[15, 37] whereas, intention to treat analysis in adult cohorts have found corticosteroids to be superior to EEN,[26, 38, 39] however, per protocol outcomes may be more similar.[15] The aim of this study was not to repeat previous research but to assess the feasibility and effectiveness of EEN and a combined EEN and PEN regimen. These pilot study results cannot be compared directly with the current standard treatment for mild to moderate adult CD, but the outcomes are of interest to patients and clinicians interested in trialing nutrition-based treatments.

No single CD treatment is effective for all patients; like-wise nutrition-based therapies are unlikely to be appropriate for all patients either. For patients who are interested in using a nutritional approach, or who want to avoid using corticosteroids, EEN and PEN therapies are a feasible treatment option. In these modest cohorts of young adults with active CD, the data indicate that EEN effectively reduces clinical symptoms and markers of inflammation within the first two weeks of treatment. Further investigation into the potential role of a PEN regimen after an initial period of EEN is warranted, however, the composition of the food included in the regimen needs further investigation as does the impact of solid food on FC and mucosal healing. EN therapy is a feasible and effective option to treat active CD in young adults who have finished secondary education and could be offered to patients interested in using a nutritional therapy approach.

## Declaration of Interests

The authors have no conflicts of interest

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442 **Figure Legends**

443 Figure 1. Flow chart of patients treated with exclusive and partial enteral nutrition.

444 EEN, exclusive enteral nutrition; EN, enteral nutrition; PEN, partial enteral nutrition

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446 Figure 2. Clinical parameters at baseline and after two weeks exclusive enteral nutrition

447 treatment (n = 33).

448 CRP, c-reactive protein; EEN, exclusive enteral nutrition; IGF-1, insulin-like growth factor-1

449

450 Figure 3. Clinical parameters at baseline, week 2 and week 8 of treatment of patients treated

451 only with exclusive enteral nutrition or with two weeks of exclusive followed by six weeks of

452 partial enteral.

453 CRP, c-reactive protein; EEN, exclusive enteral nutrition; IGF-1, insulin-like growth factor-

454 1; PEN, partial enteral nutrition

455